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Subject of Report: "Synthesis of gem-Disubstituted Thiazolines"

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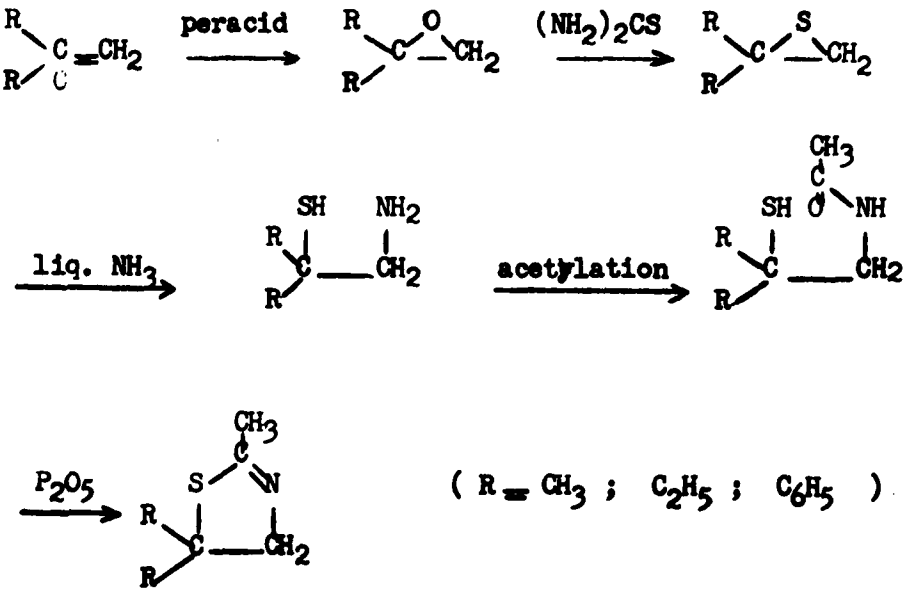
Synthsis of gem-Disubstituted Thiazolines

Preparation of 2-methyl-5,5'-dialkyl-Δ^2-thiazolines and 2-methyl-5,5'-diphenyl-Δ^2-thiazoline was undertaken according to the following genernal scheme.



Preparation of 1,1'-Disubstituted ethleneoxide

(1) 1,1'-Dimethyl-ethyleneoxide.[1]

Iso-buthylene gas(1,1'-dimethyl-ethylene; Matheson co. Inc.) was dissolved into ethyl ether with external cooling(11 g. of iso-buthylene in about 100 ml. of ether; 0.20 mole), into which 28g. (0.20 mole) of perbenzoic acid[2] in 300 ml. of ether was added. The solution was kept at 0° for 24 hrs. At the end of 24 hrs., the perbenzoic acid in the solution was analized by iodometric

titration, which shown that only the slight excess of perbezoic acid remained. The perbenzoic acid in the mixture was removed from the ether solution by shaking with an excess of 10 % NaOH solution, and then the ether solution was washed with water until the solution shown neatral, which was then dried with anhydrous sodium sulfate. The product, 1,1'-dimethyl- ethyleneoxide, was then separated by fractional distilation; b.p. 50-54° (lit.[3] 50-53°). The yield was 9-10 g. (64-70 %), I.R. spectra #1.

Titration of perbenzoic acid in the ether solution[2].

In order to estimate the amount of active oxygen in the ether solution an aliquetepart of the solution was analized as follows; one and half gram of sodium iodide was dissolved in 50 ml. of water, into which 5 ml. of glacial acetic acid and 5 ml. of ether were added. To this mixture was added 10 ml. of the ether solution of perbenzoic acid with vigorous shaking. The iodine liberated was titrated with 0.1 N sodium-thiosulfate solution. One ml. of the sodium sulfate is equivalent to 0.0069 g. of perbenzoic acid.

(2) 1,1'-Diethyl ethyleneoxide.[4]

To 23 g. (0.17 mole) of perbenzoic acid in 340 ml. of chloroform was added 14 g. (0.16 mole) of 1,1'-diethyl-ethylene(Matheson Coleman & Bell co., redistiled b.p. 66.2-66.7°) at a time keeping the temperature below zero[1]. The mixture was shaken frequently at the first hour, and was then kept in an ice box for 24 hrs. The complete disappearence of perbenzoic acid was analized by iodometric titration.

At the end of the reaction the mixture was colored yellow slightly. It was then treated as same as in the case of 1,1'-dimethyl-ethyleneoxide. The crude product was distiled at an atmospheric pressure, b.p. 102-107° (lit.[4] 104-107°). The yield was 10 g. (65 % of theoretical). I.R. # 2.

(3) 1,1'-Diphenyl -ethyleneoxide.[5]

To 23.8 g. (0.17 mole) of perbenzoic acid[1] in about 300 ml. of chloroform was added 27.4 g. (0.15 mole) of 1,1'-diphenyl-ethylene(Eastman Chemicals) at the temperature of below zero. The temperature of the reaction mixture raised suddenly at the initial which was cooled in an ice-salt bath, and was then kept in an ice-box keeping the temperature below for more than 30 hrs. Benzoic acid liberated was removed with an excess of 10 % sodium hydroxide and the alkali was washed with water several times. The crude product in chloroform solution did not crystalize, and the solution colored a slightly yellow in an open air. Separating chloroform from the solution completely by distilation, the residue remained was kept in a vacume desicator which was then cooled in an ice-box. Thus, crystals formed was recrysterized from 95% ethanol, m.p. 54-56° (lit.[5b] 56°). The yield was 15 g.(54%).

Preparation of 1,1'-Disubstituted Ethylenesulfide

(1) 1,1'-Dimethyl-ethylenesufide.[6]

To a solution of 25 g.(o.33 mole) of thiourea in 100 ml. of methyl alcohol was added 24 g.(0.33 mole) of 1,1'-dimethyl-ethyleneoxide. The mixture in a round bottom flask was stirred vigorously at room temperature for 17.5 hrs., and then the contents were poured into about 500 ml. of water. The unreacted white colored thiourea was dissolved completely, which was then transfered to a separating funnel. Standing 5-10 min. , colorless

heavy oily liquid was separated and washed with water three times, dried over sodium sulfate. The crude product was then distiled at an atmospheric pressure, b.p. 82-85° (lit.[6b] 84-86°). The yield was 9.2 g. (31%).

(2) 1,1'-Diethyl-ethylenesulfide.

The preparation of this compound was carried out according to the same method as the case of 1,1'-dimethyl-ethylenesulfide. B.p. 70-71°/73mm.; n_D^{25}, 1.3330. Analysis; I.R. # 3.

Calc.	C, 62.00(%)	H, 10.41	S, 27.59
Found	C, 61.90	H, 10.35	S, 27.40

(3) 1,1'-Diphenyl-ethylenesulfide.

1,1'-Diphenyl-ethyleneoxide was treated with thiourea in methanol solution similarly as the case of 1,1'-dimethyl-ethylenesulfide. The crude product was extracted with chloroform, which was washed with water several times to remove unreacted thiourea. The chlorofrom solution containg the product was condensed by fresh evaporation, from which sticky oil was obtained. The was then distiled, and white crystal formed from distilate was recrystalized from aceton and water mixture three times; m.p. 136-8° white micro needle type crystal. Analysis; I.R. # 8

Calc.	C, 79.19;	H, 5.70(%)
Found	C, 79.34;	H, 5.64

Ammonolization

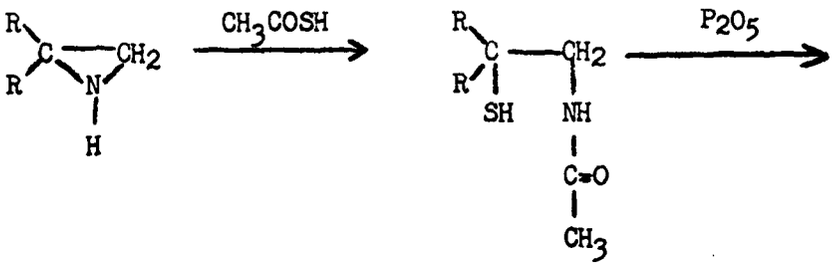
In order to prepare 1,1'-disubstituted aminomercaptan, 1,1'-disubstituted thiirane was treated with sodium amide in liquid ammonia solution. To 5.6 g. of 1,1'-dimethyl thiirane in an excess amount of liquid ammonia was added the equivalent amount of sodium amide in a steel-lined sealed tube at room temperature for more than 36 hrs. Keeping the sealed tube cold in a trichloroethylene-dryice bath the tube was opened carefully, and then equivalent amount of ammonium chloride was added into the mixture. evaporating all of ammonia gas by standing at room temperrature, the residure was treated with ether to extract out ammonium sa;t of the amino-mercaptan. The ether filtrate was then saturated with anhydrous HCl gas, from which a tar-like black oily product was obtained. Then it had been tried to crystalize from various organic solvents. However, it was never crystalized in every efforts. The residure filtrated from the ether solution was also treated with aq. HCl solution, which was reacted vigorously. It was very likely that the HCl solution reacted with unreacted sodium amide, which was found that by metal fusion and m.p. that sodium chloride was formed; including some other impurity, most likely inorganic compounds. The ammonolization, three membered ring opening of gem-disubstituted thiirane(gem-dimethyl, gem-diethyl and gem-diphenyl) with ammonia was carried out under various reaction condition many times. The results of every case were unsatisfactory and failed. The summery are as follows:

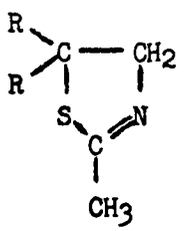
Substituted Thiirane	Solvent & Reactant	Temp.	Time	Products
gem-Dimethyl	liq. NH_3 with $NaNH_2$	Rm.	36(hrs.)	Tar, NaCl & inorganic inpurities
gem-Dimethyl	NH_3 only	Rm.	48	Same as above
gem-Diethyl	liq. NH_3	60°C	20	Explode
gem-Diethyl	liq. NH_3	Rm.	20	White granulate solid, m.p. 93-95° analysis Calc. C,54.08; H,11.35; N,10.51; S,24.06 Foud. C,60.93; H,10.34; N, 1.95; S,27.34 I.R. # 4
gem-Diethyl	liq. NH_3	Rm.	20	HCl salt, m.p. 162-4° Metal fusion test; (1) No nitrogen (2) Contained S I.R. #4 5, no C-N, N-H band; analysis, Cacl. C,42.46; H, 9.51 Cl,20.89; N,8.25 S,18.89 Found C,57.83; H,10.03 Cl,25.49; N,1.92 S,24.40
gem-Diethyl	liq. NH_3 in Chloroform	Rm.	24	Mixture of inorganic compounds
gem-Diethyl	Reflux by cooling condenser with liq. NH_3		8	Ninhydrin for NH_2 and sodium nitroprusside test for SH were both negative; I.R.#1
gem-Diphenyl	liq. NH_3 in chloroform under N_2 gas	Rm.	24	Electropholysis for NH_2 negative; I.R. and m.p.(141° original 138° proved starting material recovered

gem-Diphenyl	liq. NH_3, $NaNH_2$ in triethyl amine	Reflux (b.p. 89.5°)	12	Mix. of inorganic substances
gem-Diphenyl	Bubbled NH_3 gas in $CHCl_3$ under N_2 gas	Rm.	24	Recovered starting material
gem-Diphenyl	Bubbled NH_3 in $CHCl_3$ under N_2	Reflux ($CHCl_3$ b.p. 61°)	24	Recovered starting material
gem-Diphenyl	Bubbled NH_3 in DMF under N_2	Reflux (b.p. 153°)	24	Recovered starting material
gem-Diphenyl	liq. NH_3 in $CHCl_3$ with $NaNH_2$	Reflux (61°)	12	Recovered starting material

Ring Opening of gem-Disubstituted Ethyleneimine with Thiolacetic Acid

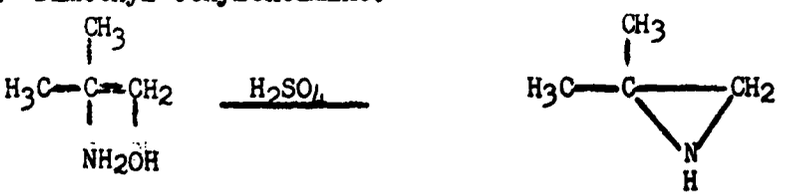
Since every efforts of ring opening of the gem-disubstituted thiirane, an alternative method[7] has been undertaken for the synthesis of 2-methyl-5,5'-gem-disubstituted-Δ^2-thiazolines. The general scheme is as follows:





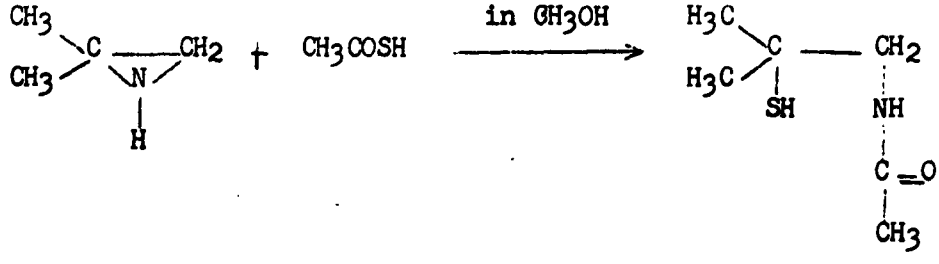
Preparation of 2-Methyl-5,5'-dimethyl-Δ^2-thiazoline

(1) 1,1'-Dimethyl-ethyleneimine.[8]



To a solution of 100 g.(1.1 mole) of 2-methyl-2-amino-1-propanol in 200 ml. of water was added with shaking 110 g. (1.1 mole) of H_2SO_4 in 200 ml. of water. The solution was distiled at atmosphilic pressure until the temperature of the reaction mixture reached 115°, and then at 25-30 mm. (water suction) and kept to boil until the temperature reached 170°. (Caution: at the temperature of 170°/20-25 mm. the mixture should not be over-heated. If the temperature raises higher than 180° the mixture changed a brown solid-like paste.) The reaction mixture became very sticky but clear. The container was cooled slowly by standing at room temperature, then a slightly brown crystalline like mass was obtained. Into this product was added an excess amount of 40% NaOH solution and the mixture distiled until the temperature of the vapor reached 100°c. Saturating the distillate with KOH organic layer appeared on upper layer. Separated and dried with KOH and then distiled twice. Collected 69-73° range (lit.[8] b.p. 69-70°), bad order. The yield was 46 g. (65% of theoretical). I.R. #6.

(2) 1,1'-Dimethyl-2-acethyl-aminomercaptan.[7a]



To 50 g.(0.65 mole) of thiolacetic acid was added 46 g.(0.65 mole) of 1,1'-dimethyl-ethyleneimine in 340 ml. of methanol by dropwise at 5-10°C. The addition of 1,1'-dimethyl ethyleneimine took about 15 min.

The mixture was then refluxed for an hour. Evaporating the methanol in the mixture completely, the contents became very sticky, colorless oil ; it was then solidified immediately in an open air. The yield was more than 95%, very soluble in water than ethanol. It is also soluble in ether and aceton. Recrystalized from ethyl ehter, m.p.72-73°. Sodium nitroprusside test for SH and ninhidrin test for NH_2 were both positive. I.R. #7. Analysis;

Calc.	C, 48.94;	H, 8.90;	N, 9.51;	S, 21.77
Found	C, 48.94;	H, 9.03;	N, 9.41;	S, 21.75

(3) 2-Methyl-5,5'-dimethyl-thiazoline.(Ring closing of 1,1'-dimethyl-2-acethylamino mercaptan)

Into a 500 ml. round bottom flask connected with a condenser was placed 2 g. of 1,1'-dimethyl-2-acethylaminomercaptan and 2 g. phosphorous pentaoxide without any solvent. The mixture was then heated on a water bath for an hour. The mixture was changed to dark brown, which was then extracted with ethyl ether; dried with sodium sulfate. Evaporating the ether, the dark brown colored oil remained was then distiled under vacume, b.p. 50-51°/10 mm. U.V. spectra shown an intensive peak at 340mu. Undoubtedly this is the compound.

Preparation of

2-Methyl-5,5'-diphenyl-Δ^2-thiazoline

(1) Acetophenone oxime.[9]

$$C_6H_5CCH_3 + NH_2OH + NaOH \longrightarrow C_6H_5\,\underset{\displaystyle NOH}{\overset{\displaystyle |}{C}}\,CH_3$$

The mixture of 60 g. of acetophenone, 40 g. of hydroxylamine-hydrochloride in 200 ml. of 95% ethanol, 24 ml. of water and 30 g. of sodium hydroxide was refluxed for 5 hours. The reaction was vigorous at the initial, which was cooled in an ice-salt bath. The contents were poured into about 50 ml. of conc. HCl in 1 litter of water at a time. White crystals filtered were washed with cold water 3 times throughly. Dried under vacume, mp 56° (lit.[9] 58°). The yield was 90-95%.

(2) 1,1'-Diphenyl ethyleneimine.[10]

To 90 g. of 3 mole etheral phenyl magnesium bromide solution was added 20g. of acetophenone oxime in 30g. toluene by dropwise with vigorous shaking. The temperrature of the contents was carefully adjusted at 135-140°; temperature of an oil bsth was 160°. The initiation of the reaction was very vigorous. Completing the addition of the oxime solution, the stirring was continued for another 30 min. After it was cooled by standing in an open air, the ether and the toluene in the mixture were evaporated completely. The contents remained were poured into a mixture of ice and ammonium chloride granular. The mass was extracted with ether, which was then washed with water thoroughly and condensed; crystalized in an ice-box. Recrystalized from aquous ethanal solution four times, m.p. 66-67.5°. Analysis;

Calc.	C,86.12;	H, 6.71;	N, 7.17
Found	C,93.02;	H, 6.53;	N, 0.29

This is not the correct compound.

References

1. H. Hibbert and D. Burt, Org. Syn., Coll. Vol. 1, 494(1941).

2. G. Braun, Org. Syn., Coll. Vol. 1, 431(1941).

3. W. Ipatiew and W. Leontowitsch, Ber., 36, 2018.

4. R. Dalebroux and H. Wuyts, C. 1906, II, 1179.

5.(a) A. Klages and J. Kessler, Ber.,39, 1754(1906).

(b) C. Paal and E. Weidenkaff, ibid., 39, 2062(1906).

6.(a) C.C.J.Culvenor, W. Davies and K.H. Pausacker, J. Chem. Soc., 1946, 1050.

(b) H. R. Snyder, J. Am. Chem. Soc., 69, 2674(1947).

7.(a) Houben-Weyl, Methoden Der Organichen Chemie, Vol. 9, 22(1955).

(b) R.Kuhn, G. Quadbeck and U.E. Rohn, Ber., 86, 468(1953); ibid., 84, 844(1951).

8. T. L. Cairns, J. Am. Chem. Soc., 63, 871(1941).

9.(a) A. Janny, Ber., 15, 2781.

(b) W. L. Semon, V. R. Damerell, J. Am. Chem. Soc., 46, 1292(1924).

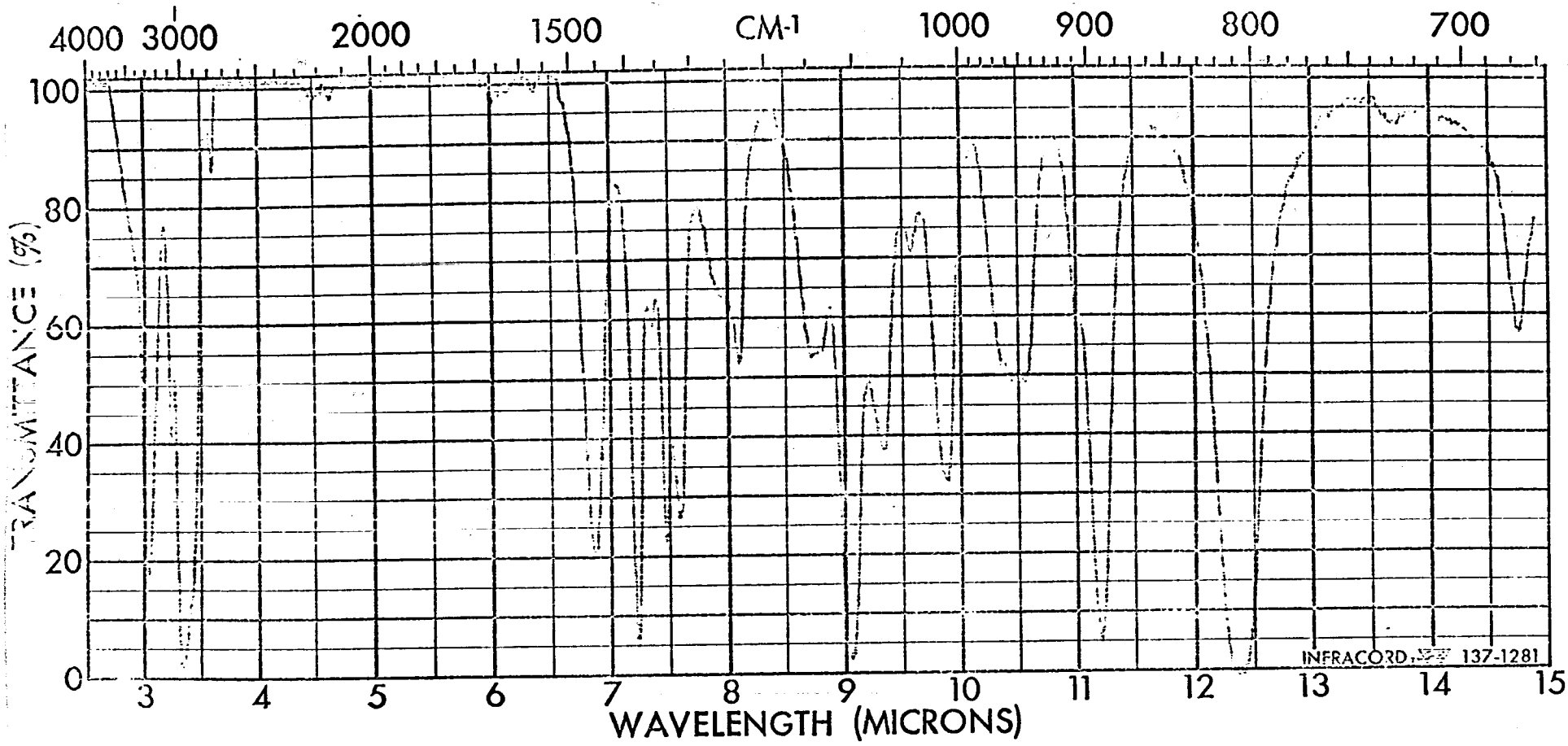
(c) , J. Chem. Soc., 121, 868.

(d) J. Lachman, Org. Syn. Coll. Vol. 2, p 70.

10.(a) K. M. Campbell and Mitarbb, J. Org. Chem., 8, 193(1943); ibid., 4, 198(1939).

(b) H. M. Kissman and Mitarbb, J. Am. Chem. Soc., 75, 2959(1953).

F. J. Wilson, I. V. Hopper and A. B. Crawford



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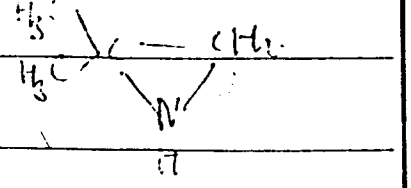	b.p. 69~72° PURITY (lit. 69~70)	2.	
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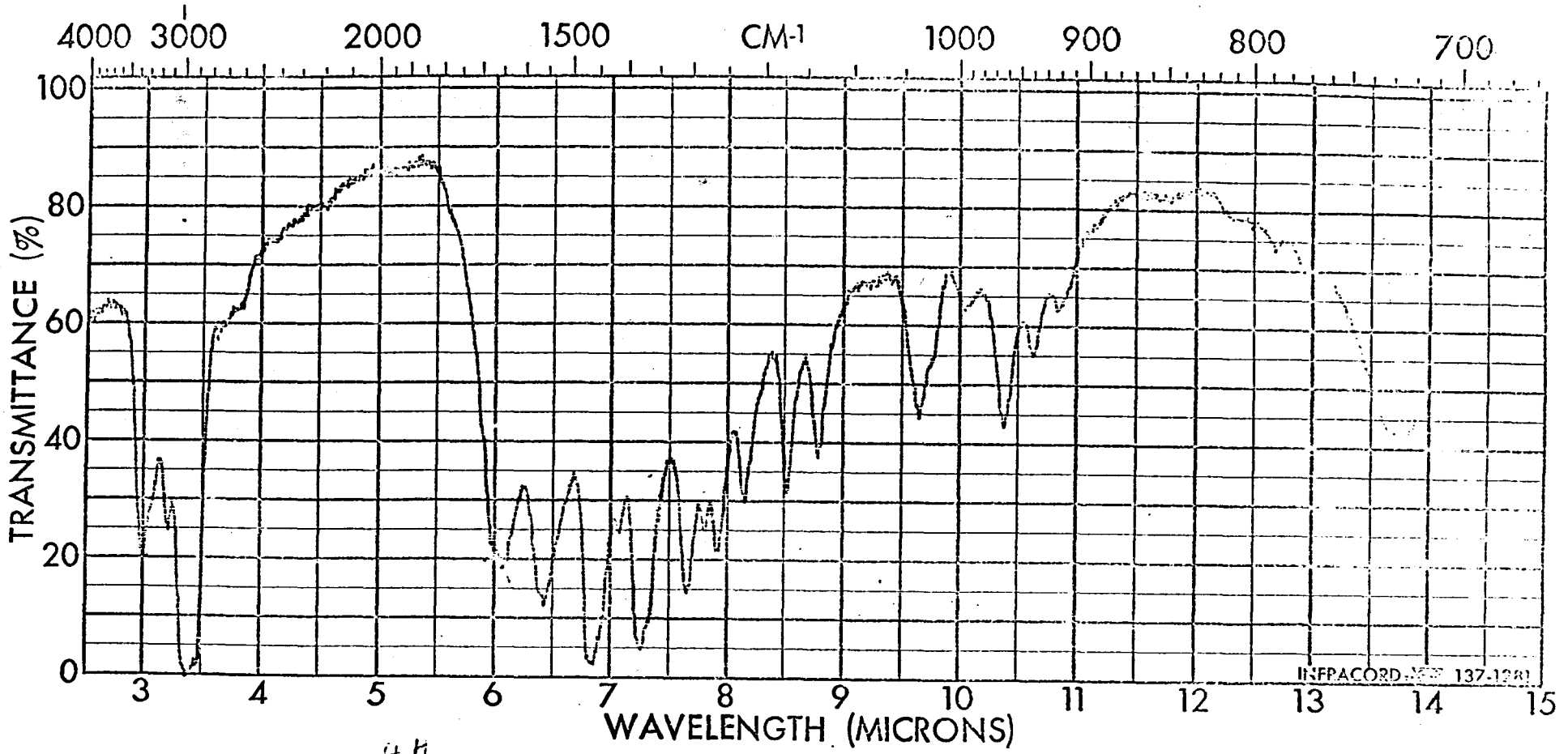

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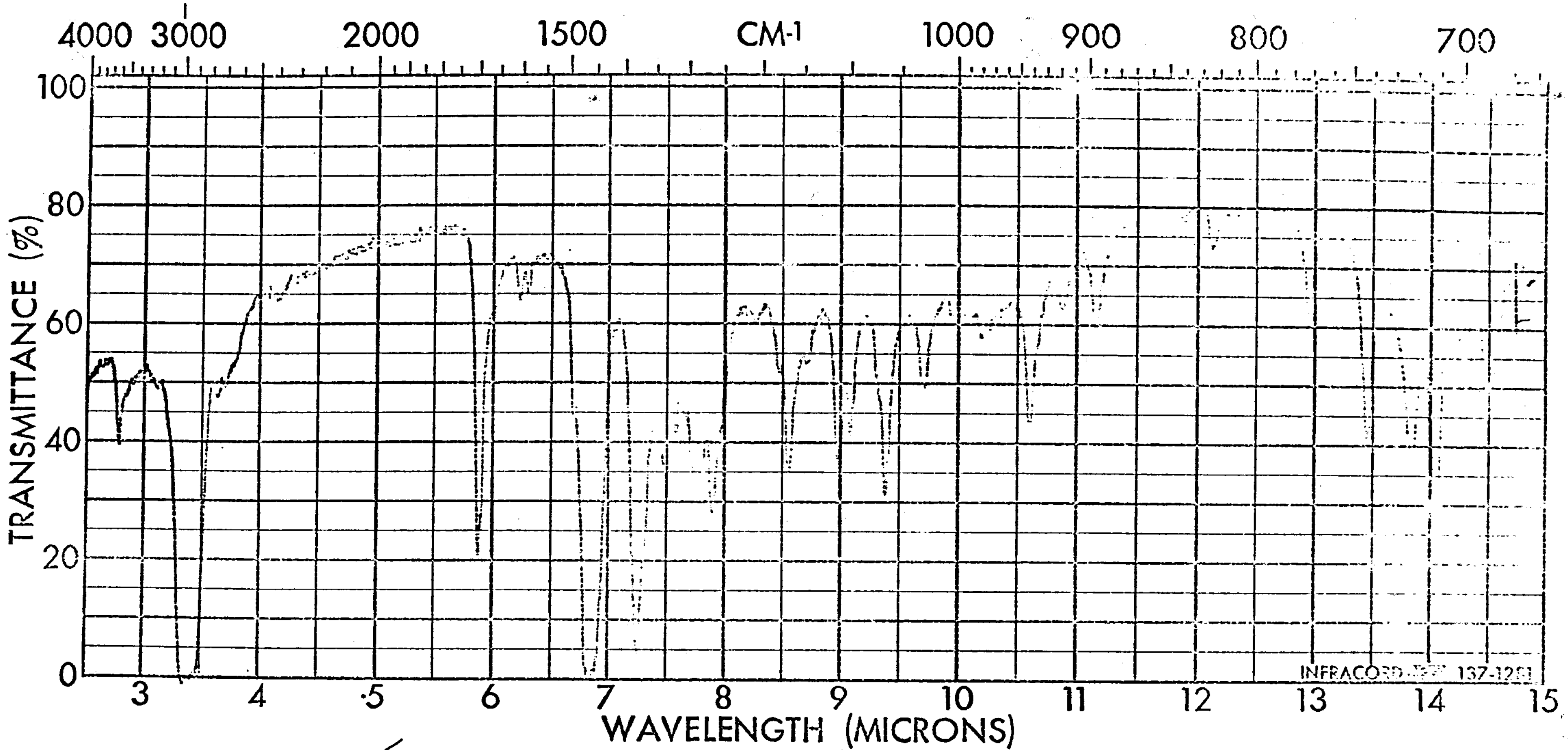

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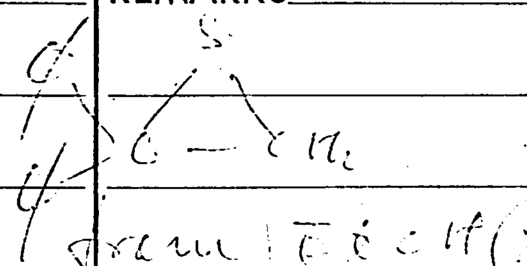
SAMPLE		1. recovered	
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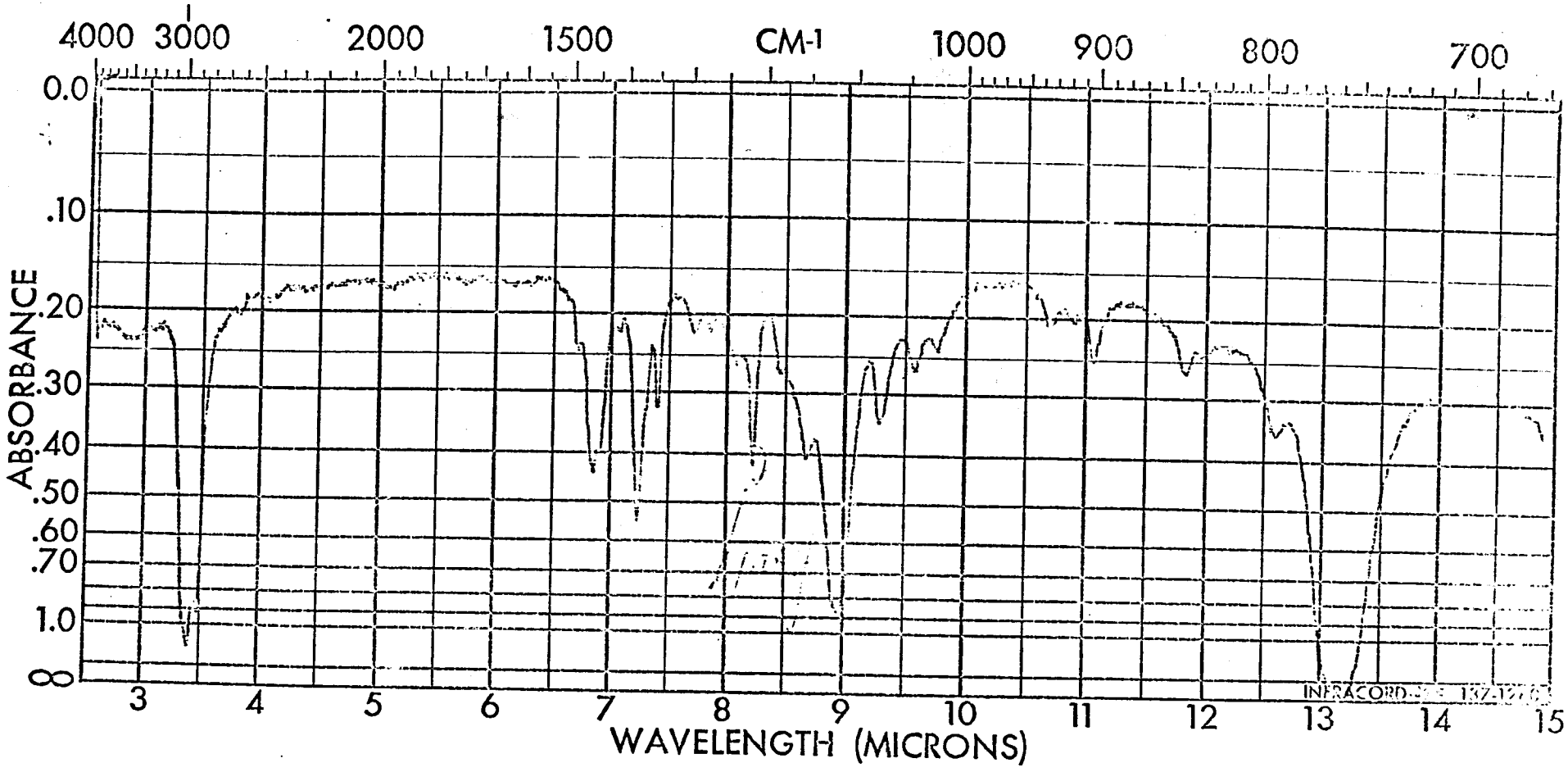

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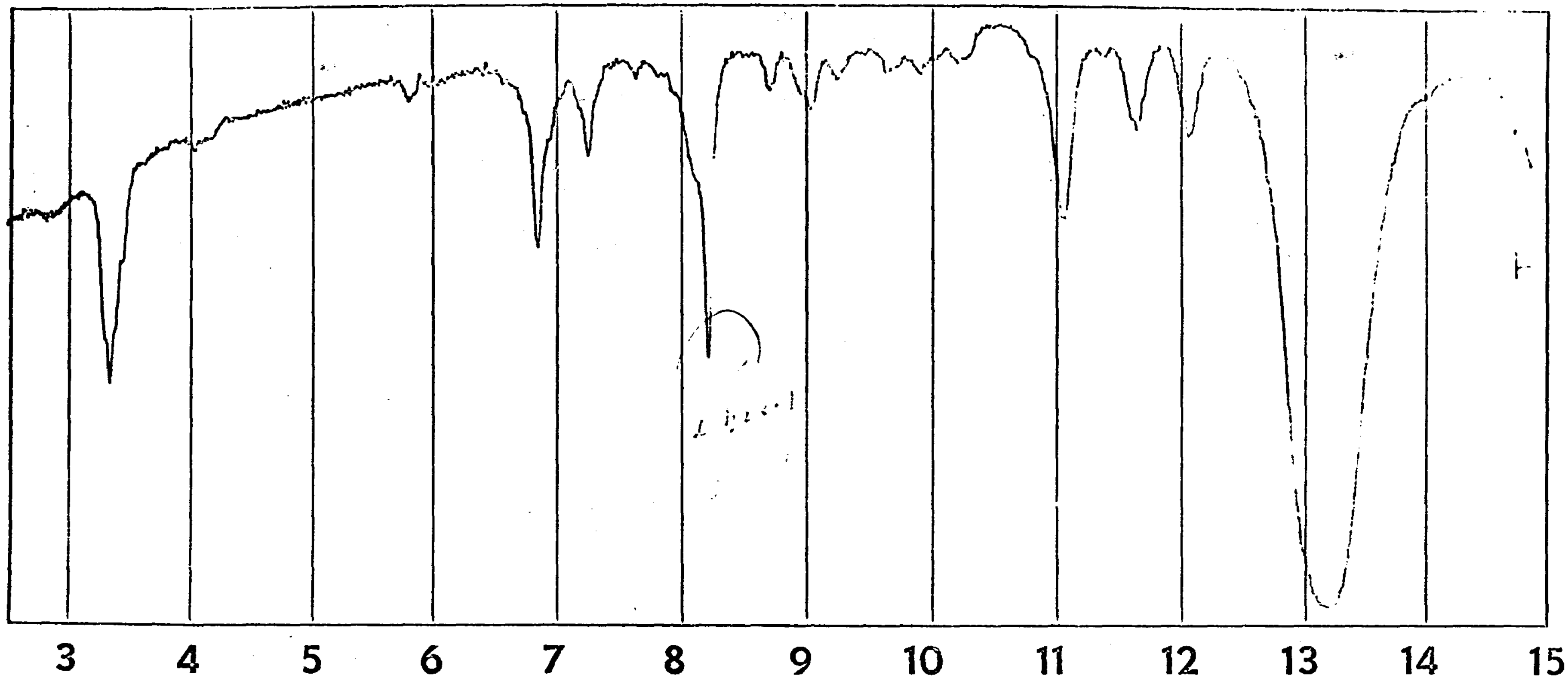

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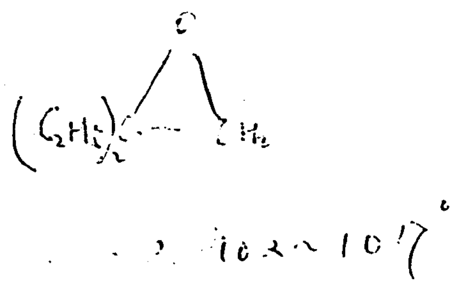

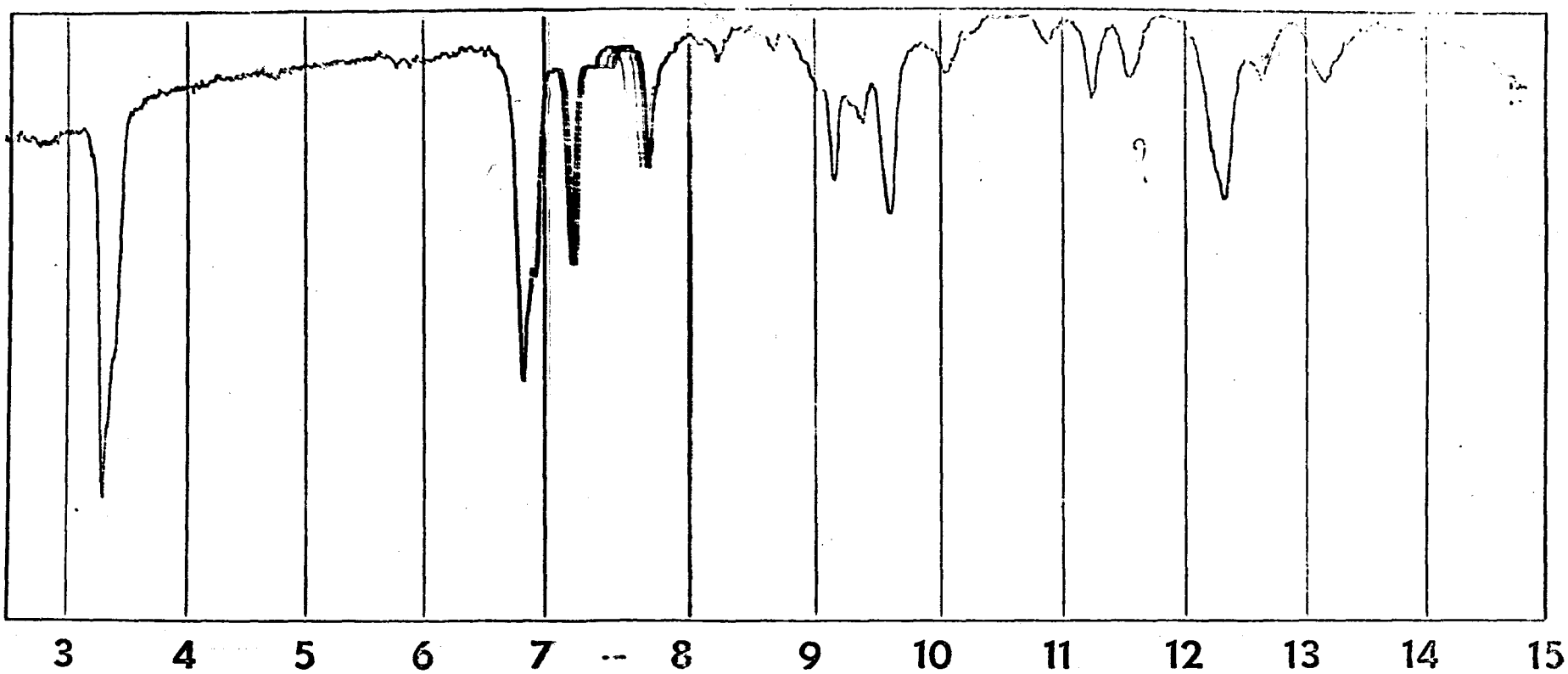

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DATE July 1, 61

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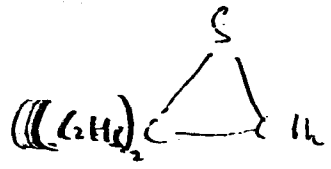

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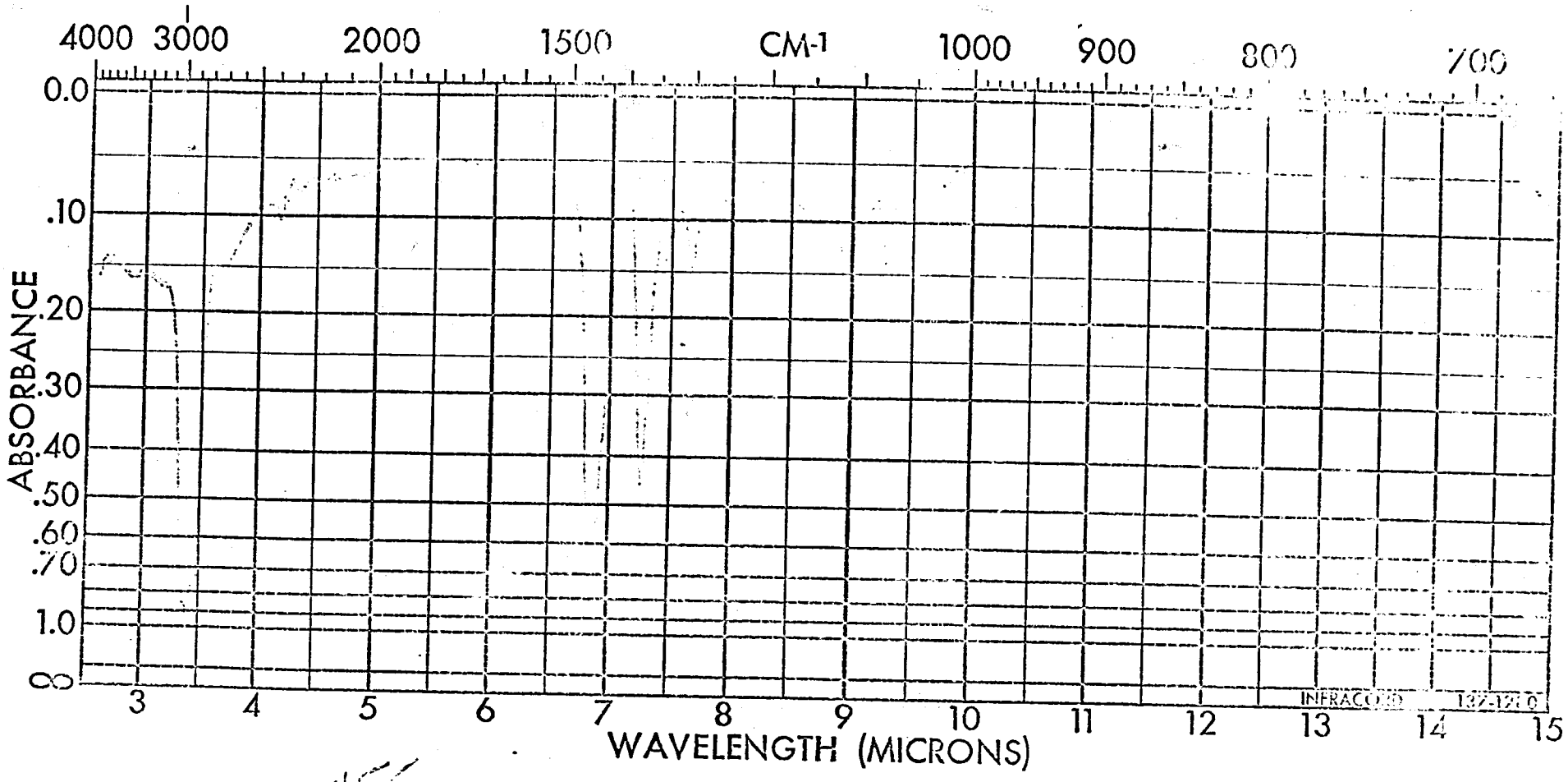
Ref. n_D^{25} = 1.3330



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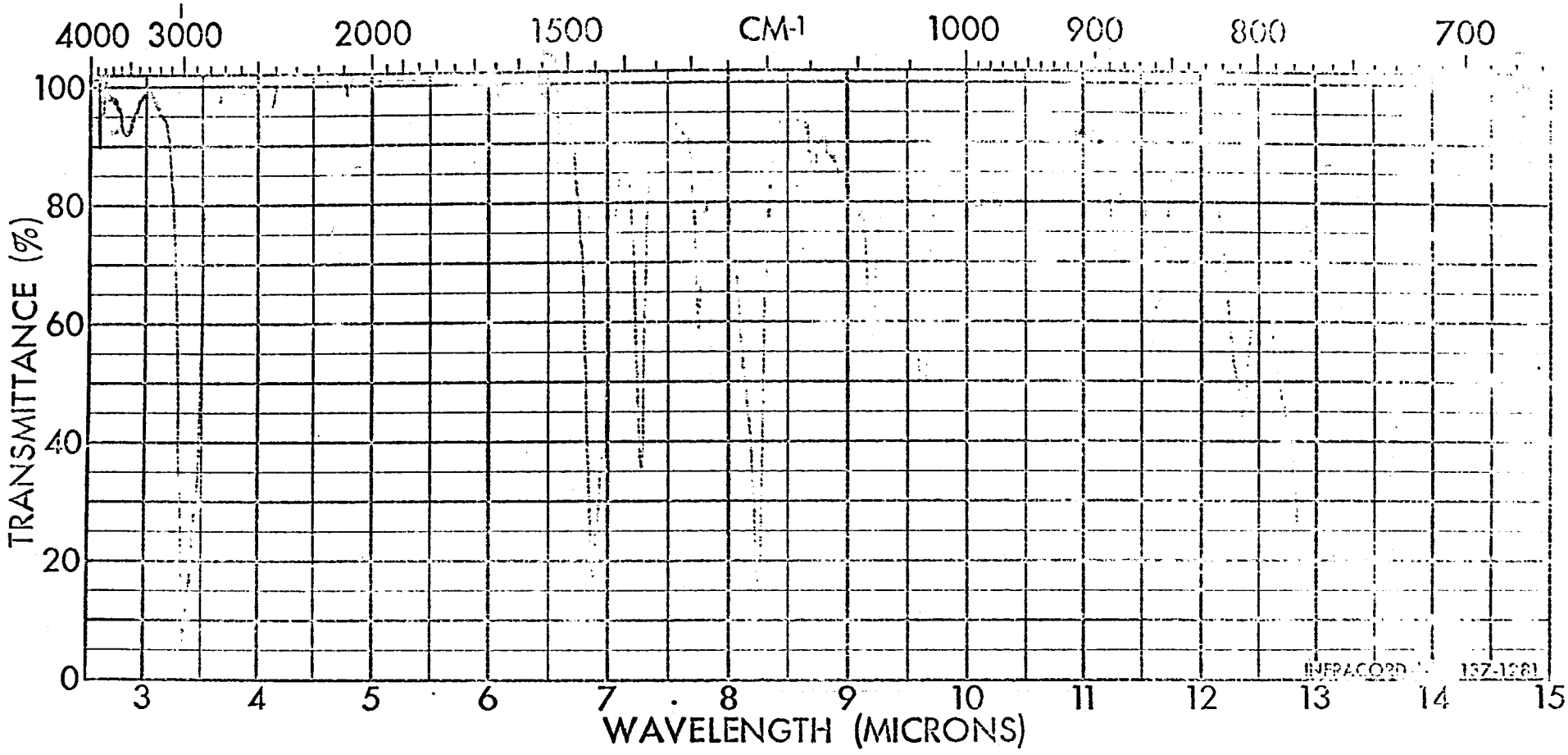

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